Objection to the Specification

In the Office Action, the disclosure is objected to because of numerous informalities. Applicant has complied with the Examiner's suggestion, and made corrections in the enclosed Substitute Specification.

Rejections under 35 U.S.C. § 112, Second Paragraph

Claim 9 stands rejected under 35 U.S.C. § 112, Second Paragraph, as being indefinite. The Examiner states that claim 9 recites "suffering from such diseases" but that no diseases are recited.

In response, Applicant submits that the claim, as amended, now recites a composition for treating or preventing specified classes of neurological diseases. Accordingly, it is believed that this ground of rejection has been obviated, and may properly be withdrawn.

Rejections under 35 U.S.C. § 102

Claims 1-9 stand rejected under 35 U.S.C. 102(b) as being anticipated by Shen et al (US 3,674,884). The Examiner states that Shen "discloses a genus of 5-amino-salicylic acid derivatives encompassing the instant claimed genus". The Examiner further states that "compounds such as 5-(p-fluorobenzylamino) salicylic acid are exemplified", and that "the corresponding benzoyl compounds such as 5-(4-nitrobenzoyl)amino salicylic acid are disclosed as well" by Shen. Further, the Examiner states that the administration of these compounds is also anticipated in therapeutically effective amount, and therefore the instant claimed use as a neuroprotectant is inherently anticipated by the disclosure of Shen.

With respect to claim 1–4, this rejection has been obstructed by the foregoing amendments by deleting the overlapped compounds. Thus, the amended claims 1-4 are not anticipated by USP 3,674,844 to Shen.

With respect to claims 5-6 and 8-9, Applicant respectfully asserts that the Examiners' characterization of the Shen reference is in error. Shen discloses

compounds that are used for treating inflammation by reducing inflammation and relieving pain in such diseases as rheumatoid arthritis, osteoarthritis, gout, infectious arthritis and rheumatic fever. In contrast, the claimed invention is directed to prohibiting central neurons from injuries caused by activation of NMDA glutamate receptors by entry and accumulation of Zn^{2+} or free radicals. In particular, the present invention is directed to the inhibition of neuronal death caused by excess activation of NMDA glutamate receptors. The instant compounds completely block NMDA-induced neuronal death, resulting in protection of central neurons from acute or chronic injuries to central nervous system (CNS) caused by activation of NMDA glutamate receptors. Conventional anti-inflammatory drugs such as NS398, nabumetone, and indomethacin, do not block NMDA-induced neuronal death.

Moreover, the compounds of the present invention are used for protecting central neurons from acute or chronic injuries to the central nervous system (CNS) caused by entry and accumulation of Zn^{2+}. Evidence is being accumulated that Zn^{2+} can mediate a neurodegenerative process in the brain of the patient suffering from seizures, ischemia, trauma and Alzheimer's disease. Accordingly, release of Zn^{2+} from the presynaptic terminal and its translocation into target neurons (i.e., entry of Zn^{2+}) triggers neuronal death. It is reported that the maneuvers which interfere with Zn^{2+} entry such as blockers of voltage-gated calcium channel or chelators can prevent Zn^{2+} neurotoxicity. For instance, Applicant recently found that aspirin prevented Zn^{2+} neurotoxicity by inhibiting Zn^{2+} entry (Kim et al., Attenuation of Zn^{2+} neurotoxicity by aspirin: role of N-type Ca^{2+} channel and the carboxylic group, Neurobiology of Disease, 2001, in press). Accordingly, the compounds of present invention seemingly prevent Zn^{2+} neurotoxicity by the same mechanism with that of aspirin. Nonetheless, Shen et al. does not provide any evidence showing that anti-inflammatory drugs can regulate Zn^{2+} neurotoxicity. Thus, a person skilled in the art would not inherently recognize that the anti-inflammatory compounds of Shen possess the action of the compounds of present invention.

Furthermore, the compounds of the present invention are used for protecting central neurons from acute or chronic injuries to the central nervous

system (CNS) caused by generation of free radicals. That is, the compounds may scavenge free radicals produced in degenerating brain areas following hypoxic-ischemia or traumatic brain and spinal cord injuries, so that neuronal loss may be reduced. However, the disclosure of Shen et al. does not describe at all that the compound may be used as an antioxidant in the degenerating brain areas, but describes only the anti-inflammatory action in inflammation of a joint. A person skilled in the art would not recognize easily that anti-inflammatory agents are oxygen radical scavengers. Although some of the oxygen radical scavengers may be used as one example of antiinflammatory agents, it is not supported from knowledge in the art that all antiinflammatory agents may be used as oxygen radical scavengers.

Therefore, the administration of the claimed compounds for the protection of central neurons from injuries caused by excess activation of NMDA glutamate receptors is not inherently anticipated by the disclosure of Shen. Nothing in Shen teaches or suggests that the anti-inflammatory agents disclosed therein would have such properties.

Thus, the present invention is distinguishable from Shen, and the rejection is therefore improper and should be withdrawn.

Rejections under 35 U.S.C. § 103

Claims 5-9 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Spector and further in view of Kumamoto et al and further in view of Shen et al. The Examiner states that Spector (The journal of Pharmacology and Experimental Therapeutics, 1974 188(2) page 55-65) alludes that para-aminosalicylic acid (PAS) has been used for treating neuronal diseases because Spector discloses a study of the concentration of para-aminosalicylic acid in cerebrospinal fluid. Moreover, Kumamoto (Japanese Journal of Pharmacology 1997, 95, pages 187-189) teaches that aminosalicylates may scavenge the oxygen derived free radicals. The Examiner concludes that by the documents of Spector and Kumamoto, one skilled in the art may be motivated to use aminosalicylates as a

scavenger of oxygen derived free radicals in the brain area such as in cerebrospinal fluid.

The Examiner further states that Shen teaches a genus of 5-amino-salicylic acid derivatives for administration as therapeutic compounds. Therefore, according to the Examiner it would have been obvious for one of ordinary skill in the art to realize that oxidative stress and associated cerebral disease could be treated with the PAS derivatives.

The Examiner's contention is respectfully traversed. The present invention is directed to compounds that have triple neuroprotective actions (as discussed above) which can not be obtained only by the aminosalicylate moiety. Neither Spector, Kumamoto nor Shen describe any inhibitory effect on neuronal death by activation of NMDA glutamate receptor, or by Zn^{2+} entry or accumulation nor the administration the claimed compounds. As shown in figure 1 in the specification, 5-amino-salicylic acid (AS) reduced neither NMDA-induced neuronal death nor Zn^{2+} neurotoxicity. Therefore, contrary to the Examiner's assertion, these aspects of the present invention can not be motivated from the prior arts of record.

In addition, the Examiner states since the claimed compounds include 5-aminosalicylate moiety, a person skilled in the art would recognize that the claimed compounds may be used as scavengers of oxygen free radicals.

In response, the Applicant asserts that the present invention shows that the claimed compounds possess much better antioxidant effects than 5-aminosalicylic acid, and that the improved antioxidant property arises from replacing the amino group of 5-aminosalicylic acid with an amino group substituted with a phenyl group or substituted phenyl group. That is, as shown in figure 1b of the specification, 5-aminosalicylic acid (AS) blocked Fe^{2+}-induced free radical neurotoxicity at a concentration of 300 μm (Figure 1b). Additionally, as shown in figure 2(b) to 15(b) in the specification, the claimed compounds blocked Fe^{2+}-induced free radical neurotoxicity at doses of 1 to10 μm. The antioxidant effects of the claimed compounds possess more potent antioxidant effect than vitamin E, known as one of the most potent antioxidants, which blocks Fe^{2+}-induced free

radical neurotoxicity at doses of 30 to100 μm and has been used to treat Alzheimer's disease, Parkinson's disease, and Huntigtion's disease (Gilgun-Sherki et al., Neuropharmacology 40:959-975, 2001; Won et al., Neurobiology of Disease 7:251-259, 2000).

However, neither Shen, Kumanmoto, nor Spector disclose or suggest the improvement of antioxidant effect that may be achieved by replacing the amino group of 5-aminosalicylic acid to the amino group substituted with a phenyl group or substituted phenyl group. Consequently, the unexpectedly superior antioxidant effects of the claimed compounds, which render them particularly well suited for the efficient treatment of oxidative stress in various neurological disorders would not have been obvious to one skilled in this art from the art of record.

Thus, the references of Spector, Kumamoto and Shen do not support a prima facie case of obviousness, and therefore the rejection under 35 U.S.C. 103(a) should be withdrawn.

CONCLUSION

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicant therefore respectfully requests that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. It is believed that a full and complete response has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Response is respectfully requested.

Respectfully submitted,

SHANKS & HERBERT

By: _____

Ping Wang

Reg. No. 48,328

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TransPotomac Plaza
1033 N. Fairfax Street
Suite 306
Alexandria, VA 22314
(703) 683-3600